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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,090	RICHARDS ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,10-12,14,16,17,19-21,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10-12,14,16,17,19-21,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/7/2005*. 8/18/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 5/12/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/13/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are pending in the application.

Response to Priority

Applicant has pointed to support for the instant claims in PCT/US03/05028. The effective filing date of the instant claims is therefore determined to be 2/20/2003, the filing date of PCT/US03/05028.

Applicant asserts that application 60/363,124 supports the claimed invention and that PCT/US03/05028 is filed within one year of 60/363,124. However, the statement of

priority of application 60/363,124 does not provide a link to PCT/US03/05028, but rather provides a link to the instant application, which was not filed within one year of 60/363,124.

Response to Arguments--Claim Rejections - 35 USC § 103(a)

The 35 U.S.C. 103(a) rejection of record has been withdrawn because applicant has raised 35 U.S.C. 103(c) and provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as Morrissey et al. (US 2003/0206887 A1) at the time this invention was made, or was subject to a joint research agreement at the time this invention was made.

Response to Arguments—Double Patenting

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application 10/919,866 for the reasons of record set forth in the office action mailed 8/8/2005.

Applicant has requested to defer addressing this rejection until the claims are otherwise in condition for allowance.

New Objections/Rejections

Claim Objections

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are objected to because of the following informalities: Claim 1 recites, "short interfering nucleic acid (siRNA)". The term "siRNA" is not an appropriate abbreviation for "short interfering nucleic acid". Amendment to recite, "short interfering ribonucleic acid (siRNA)" or "short interfering

nucleic acid (siNA)" would obviate this objection. Claims 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are objected to because they depend from claim 1.

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 3 recites, "wherein said siRNA molecule comprises one or more ribonucleotides". Since the claim is drawn to a siRNA, the molecule by nature comprises one or more ribonucleotides. Therefore, claim 3 fails to further limit claim 1.

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are objected to because of the following informalities: Part (c) of claim 1 recites, "one or more pyrimidine nucleotides present one or both strands". It appears that applicant has inadvertently omitted the word "in" between "present" and "one". Appropriate correction is required. Claims 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are objected to because they depend from claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell, 2000, Vol. 6, pages 1077-1087), as further evidenced by Zhang et al. (Cell, 2004, vol. 118, pages 57-68).

The invention of the above claims is drawn to a chemically synthesized siRNA comprising a sense and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length and the antisense strand comprises nucleotide sequence that is complementary to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305 and one or more pyrimidines present in one or both strands is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. The invention is further drawn to a composition comprising the siRNA and a carrier or diluent.

Parrish et al. teach that RNAi requires duplex formation between the two trigger strands of RNA, and that the duplex must include a region of identity between the trigger and the target RNA. Parrish et al. teach that duplexes comprising sense and antisense strands as short as 26 bp can trigger RNAi.

It is noted that instant claim 1 does not require for the siRNA to have any specific relationship to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305 other than to comprise "nucleotide sequence that is complementary" to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305. Therefore, in absence of a structural limitation necessitating specific targeting, the siRNA only needs to comprise any nucleotide sequence that is complementary to CHRM3.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length, and the antisense strand "comprises nucleotide sequence"

that is complementary to a CHRM3 nucleotide sequence comprising instant SEQ ID NO: 305 (see the first duplex of Figure 1B of Parrish et al., wherein the nucleotide sequence of nucleotides 12-14 of the sense strand are identical to nucleotides 8-10 of instant SEQ ID NO: 305).

Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications. Although Parrish et al. do not specifically teach 2'-deoxy-2'-fluoro modifications of the 26bp duplex, the long dsRNA taught by Parrish et al. trigger RNAi and were necessarily cleaved into dsRNA duplexes 21 nt in length.

As evidenced by the post-filing art of Zhang et al., Dicer is a multidomain ribonuclease that processes dsRNAs to 21 nt siRNAs during RNA interference. Zhang et al. teach that Dicer has one processing center and generates products with 2 nt 3' overhangs. Although Parrish et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes 21 nt in length with 2 nt 3' overhangs, the long dsRNA molecules taught by Parrish et al. were necessarily cleaved into such duplexes comprising 2'-deoxy'-2'fluoro modifications, as instantly claimed. Additionally, Parrish et al. teach injection mixes comprising compound.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered

by *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Since Parrish et al. teach administering dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated by the activity of Dicer, which cleaves long dsRNA into 21 nt fragments with 2 nt 3' overhangs, the teachings of Parrish et al. anticipate the instant invention. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc., 251* F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". This is considered to inherently anticipate the compound even though the compound's existence was not known.

Therefore, the instant invention is anticipated by Parrish et al., as further evidenced by Zhang et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 14, 16, 17, 19-21, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce (WO 99/13886), in view of Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco et al. (US 6,346,398 B1), Hammond et al. (Nature,

2001, Vol. 2, pages 110-119), and Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86).

The invention of the above claims is drawn to a chemically synthesized siRNA comprising a sense and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length and the antisense strand comprises nucleotide sequence that is complementary to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305 and one or more pyrimidines present in one or both strands is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. The invention is further drawn to modifications of the siRNA and to a composition comprising the siRNA and a carrier or diluent.

Nyce teaches antisense oligonucleotides that attenuate the expression of target mRNA. The oligonucleotides are preferably up to about 30 nucleotides in length, more preferably up to about 21 nucleotides in length (see page 16). Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (see page 54). Nyce teaches phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73) for enhancing the uptake of the oligonucleotides. The 100% substituted oligonucleotide comprises a phosphorothioate at the 3' end. Nyce teaches compositions comprising the oligonucleotide and a pharmaceutically acceptable carrier (see page 77). Nyce teaches surfactants or surfactant components bound to the 5' and/or 3' ends or the oligonucleotides for enhancing uptake of the oligonucleotide (see page 80), meeting the instant limitation of "terminal cap".

Nyce does not teach double stranded siRNAs, 2'-deoxy-2'-fluoro modifications, linkers or inverted deoxy abasic moieties.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length, and the antisense strand "comprises nucleotide sequence" that is complementary to a CHRM3 nucleotide sequence comprising instant SEQ ID NO: 305 (see the first duplex of Figure 1B of Parrish et al., wherein the nucleotide sequence of nucleotides 12-14 of the sense strand are identical to nucleotides 8-10 of instant SEQ ID NO: 305).

Parrish et al. teach dsRNA duplexes with 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand of (see figure 5). Parrish et al. teach 26bp duplexes that mediate RNAi. The long dsRNA taught by Parrish et al. trigger RNAi and were necessarily cleaved into dsRNA duplexes 21 nt in length, as explained in the 35 U.S.C. 102(b) rejection above.

Elbashir et al. teach chemically modified 21-nucleotide siRNA duplexes that mediate RNA interference. The duplexes taught by Elbashir et al. comprise an antisense and a sense strand. Elbashir et al. teach 2'-O-methyl and 2'-deoxy modified siRNA duplexes (see page 6881). Elbashir et al. teach that the most efficient triggers of RNAi are duplexes of 21 nt siRNAs with 2 nt 3' overhangs. Elbashir et al. teach that a 5'-phosphate on the antisense strand of a siRNA duplex is required for siRNA function (see page 6886).

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides for sequence specific inhibition of a gene target. Pavco et al. teach chemical modifications

including 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

It is noted that the instant claims do not require for the siRNA to be specifically targeted to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305, but rather require the siRNA to comprise "nucleotide sequence that is complementary to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305". However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to design a siRNA, as taught by Elbashir et al. or Parrish et al., to specifically target CHRM3, as taught by Nyce.

Additionally, it would have been obvious to incorporate 2'-O-methyl or 2'deoxy modifications, as taught by Nyce and Elbashir et al., as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. and inverted deoxy abasic moieties, as taught by Pavco et al.

One would have been motivated to use a siRNA targeted to CHRM3 instead of an antisense oligonucleotide, as taught by Nyce, because Hammond et al. teach that

using dsRNA to inhibit gene expression is more sequence specific than using antisense methods and that RNAi is a more potent method, requiring only a few molecules of dsRNA per cell. One would have been motivated to target CHRM3 since Nyce specifically teaches antisense oligonucleotides targeted specifically to human CHRM3 and siRNAs are known to be preferred mediators of target gene expression, as evidenced by Hammond et al. Additionally, each of the instantly recited chemical modifications were known in the art to enhance the delivery of antisense oligonucleotides or siRNA duplexes, as evidenced by the teachings of Nyce, Elbashir et al., Pavco et al., and Parrish et al. Each of these molecules was known to face the same delivery challenges.

Further support for this is offered by Caplen, who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies, and therefore, supports the examiner's position that one would be motivated to incorporate each of the instant modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

Finally, one would have a reasonable expectation of success given that Nyce et al. teach antisense oligonucleotides specifically targeted to human CHRM3, the instant target, and siRNA duplexes were known to be preferable inhibitory molecules, as taught

by Hammond et al. Furthermore, Elbashir et al. teaches that siRNA duplexes can be designed to inhibit target gene expression in a sequence specific manner. Since siRNAs were known to be preferable inhibitory molecules and it was known to target CHRM3 with an antisense oligonucleotide, one would reasonably expect for a siRNA targeted to CHRM3 to be successful. Additionally, one would have a reasonable expectation of success that the instantly recited chemical modifications would benefit a siRNA duplex targeted to CHRM3 because each of the modifications were known in the art to benefit antisense oligonucleotides or siRNA duplexes, each of which face the same delivery challenges.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce (WO 99/13886), in view of Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco et al. (US 6,346,398 B1), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), and Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), as explained above, further in view of Agrawal et al. (WO 94/01550).

The invention of the above claims is drawn to a chemically synthesized siRNA comprising a sense and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length and the antisense strand comprises nucleotide sequence that is

complementary to a CHRM3 nucleotide sequence comprising SEQ ID NO: 305 and one or more pyrimidines present in one or both strands is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. The invention is further drawn to modifications of the siRNA, linkers, and to a composition comprising the siRNA and a carrier or diluent.

Nyce, Parrish et al., Elbashir et all, Pavco et al, and Hammond et al. do not teach polynucleotide or non-nucleotide linkers.

Agrawal et al. teach self-stabilized oligonucleotides comprising a sense strand and an antisense strand connected via a polynucleotide linker (see figure 5, 3rd molecule, for example). Agrawal et al. teach that the oligonucleotide forms a totally or partially double-stranded hairpin structure that is resistant to nucleolytic degradation (see page 5) and that preferably the complementary region is about 50 nucleotides or less (see page 15), which would form a duplex of 25 base pairs or less. The oligonucleotides can be polymers of ribonucleotides or deoxyribonucleotides and can have a nucleotide or non-nucleotide linker (see page 15). Agrawal et al. teach phosphorothioate and 2'-O-methyl modifications. Agrawal et al. teach that such modifications increase stabilization and resistance to nucleolytic degradation without the disadvantages of oligonucleotides that are known in the art (see page 3 and 16).

It would have been obvious to one of ordinary skill in the art to incorporate polynucleotide or non-nucleotide linkers, as taught by Agrawal et al., into a siRNA molecule targeted to CHRM3, as explained in the 35 U.S.C. 103(a) rejection above.

One would have been motivated to incorporate nucleotide or non-nucleotide linkers into the siRNA because Agrawal et al. teach hairpin formations that increase stabilization and resistance to nucleolytic degradation.

Finally, one would have a reasonable expectation of success given that linkers were known in the art at the time the invention was made to increase stabilization of double-stranded oligonucleotides, as evidenced by Agrawal et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
Art Unit 1635

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PRIMARY EXAMINER